UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,772	02/25/2002	Peter Droge	DEBE:008US	4391

7590 05/04/2006

Steven L. Highlander
FULBRIGHT & JAWORSKI L.L.P.
Suite 2400
600 Congress Avenue,
Austin, TX 78701

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,772	DROGE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,32-39,43-51 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,32-39,43-51 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 2/13/06 was entered.

Amended claims 29-30, 32-39, 43-51 and 58 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, for the lack of Written Description was partially withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(a) as being anticipated by Lorbach et al. (J. Mol. Biol. 296:1175-1181, 2000, IDS) was withdrawn in light of the provision of the translated priority document.

Written Description

Amended claims 49-51 are still rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons already set forth in the Office action mailed on 4/19/05 (pages 3-6).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v.

Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's elected invention is drawn to a method of sequence specific recombination of DNA in a eukaryotic cell *in vitro* or *ex vivo*, the method comprises the steps of providing a eukaryotic cell comprising a first DNA segment with a second DNA segment, wherein the DNA segments have the limitation recited in claim 29 and wherein the cell is further provided with any modified bacteriophage λ integrase which induces sequence specific recombination through *att*B and *att*P or *att*R and *att*L sequences in the first and second DNA segments.

However, apart from disclosing two mutant bacteriophage λ integrases, Int-h (E174K) and the double mutant Int-h/218 (E174K/E218K), the instant specification fails to describe structural characteristics of any other modified bacteriophage λ integrases having functional properties similar to Int-h and/or Int-h/218 in inducing sequence specific recombination through *att*B and *att*P or *att*R and *att*L sequences. Nor does the instant specification describe any structural characteristic for any modified Int factor to be utilized in the method of amended claim 49 other than the aforementioned bacteriophage λ integrase mutants. The instant specification further fails to provide a representative number of species for a broad genus of a modified bacteriophage λ integrase or a modified Int factor.

At about the effective filing date of the present application (8/29/00), the prior art does not describe any other modified bacteriophage λ integrases or any modified Int

factor apart from the Int-h and Int-h/218 mutants as evidenced by the teachings of Hartley et al. (US 5,888,732); Crouzet et al. (US Patent 6,143,530), and Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS).

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a broad genus of modified bacteriophage λ integrases or a modified Int factor to be utilized in the methods as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Argument

With respect to the above rejection, in the Amendment filed on 2/13/06 (page 6) Applicants argued basically that Applicants traversed the rejection, but in the interest of advancing the prosecution the claims have been amended to recite the modified Int molecules Int-h and Int-h/218.

It is noted that amended claims 49-51 still recite "modified Int", not necessarily limited to the modified Int molecules Int-h and Int-h/218. Accordingly, the lack of Written description rejection is still maintained for these claims for the reasons set forth above.

Claim Rejections - 35 USC § 103

Amended claims 29-30, 32-35, 44-45, 49 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. (US 5,888,732) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS). ***This is a modified rejection containing a new ground of rejection.***

Hartley et al disclose a method of making chimeric DNA comprising the steps: (a) combining *in vitro* or *in vivo*, (b) an Insert Donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site, wherein the first and second recombination sites do not recombine with each other; (c) a Vector Donor DNA molecule containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination site do not recombine with each other; and (d) one or more site specific recombination proteins capable of recombining the first and third recombination sites and/or the second and fourth

recombination sites (see Summary of the Invention, and Figures 1-2A-F). Figure 1 depicts a general method of Hartley et al., involving two recombination events with two different recombinases that recognize different recombination sites. Hartley et al also teach that the exchange of DNA segments can be achieved by the use of various recombination proteins described in the art, including λ Integrase (col. 13, line 57 continues to line 24 of col. 16). Hartley et al further teach examples of recognition sequences to be utilized include attB, attP, attL, and attR sequences which are recognized by the recombinase enzyme λ Integrase (col. 8, lines 43-63). The disclosed attB sequence of SEQ ID NO:32 comprises the sequence that is identical to SEQ ID NO:1 of the present application, and therefore the corresponding attP recombination sequence must have the same SEQ ID NO: 2 of the present application, or at least a derivative thereof. Furthermore, the attL and attR recombination sequences that are catalyzed by λ Integrase taught by Hartley et al. must have the same SEQ ID NO:3 and SEQ ID NO:4, respectively, or at least a derivative thereof. The desired DNA segment includes a selectable marker (DNA segments that encode beta-galactosidase, GFP or cell surface proteins), an antisense oligonucleotide or a toxic gene (col. 9, lines 5-36), and that host cells include *E.coli* cell lines as well as eukaryotic cells (col. 13, lines 35-55). Hartley et al. also teach the use of integrase in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL to form attP and attB, and in effect reverse the integrative recombination between attP site and attB site mediated by λ Integrase (col. 15, lines 1-4), as well as the use of IHF proteins for the recombination at attB and attP sites (col. 14, lines 26-30). Hartley et al. also teach engineered att

recombination sites having one or multiple mutations to enhance specificity or efficiency of the recombination reaction, and that a tripartite protein fusion could be accomplished with parental plasmids containing recombination sites attR1 and attR2; attL1 and attL3; and attR3 and attL2 (col. 16, lines 26-61; col. 17, line 47 continues to line 46 of col. 18). With respect to claim 30, the method for introducing the Insert Donor and the Vector Donor into a cell is a recombinant method, and such a method would result in the random incorporation of any one of the Insert Donor and the Vector Donor in a DNA of the cell.

Hartley et al do specifically teach the use of any modified λ Integrase, specifically Int-h or Int h/218.

However, at the effective filing date of the present application Christ & Droge already taught the mutant λ Integrases, Int-h and Int-h/218, that are capable of mediating substrate deletion through λ site-specific recombination in prokaryotes in the absence of co-factors Fis and Xis (see at least the abstract; page 829, right hand column, top and bottom of the first full paragraph). Christ & Droge further teach that the potential of these mutants to perform recombination in the absence of accessory factors is due to their enhanced affinity for core sites, and that Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase (page 827, left column, second full paragraph; page 828, left column, top of last paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Hartley et al. by also utilizing the mutant λ Integrases, Int-h and

Int-h/218, of Christ & Droge in either the integrative or the excision recombination step or both for the making a chimeric DNA due to the advantages offered by these mutant Integrases, at least the mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than the wild-type Intergrase. Please also note that this modified method does not exclude the use of wild-type λ Integrase altogether in the method of Hartley et al, depending on whether the mutant Integrases would be employed in both recombination steps.

An ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Christ & Droge, at least these mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hartley et al., Christ & Droge, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect in part to the above rejection in the Amendment filed on 2/13/06 (pages 7-9) have been fully considered but they are respectfully not found persuasive.

Applicants argue mainly that Hartley et al use exclusively the **wild-type** lambda integrase, while Christ & Droge relates exclusively to integrative and excisive attL/attR and attP/attB recombination performed in **prokaryotes**. Applicants further argue that Christ & Droge does not give the slightest hint that the described modified integrase could also promote recombination events in eukaryotic cells and that it is well known that the organization of the prokaryotic genome distinct from eukaryotics. Applicants also argue that although the modified integrases of Christ & Droge are adapted without the DNA-stabilizing factor IHF and the enzyme Xis in prokaryotic cells (i.e., having a prokaryotic DNA substrate), there was no reasonable expectation of success that they would also work in eukaryotic cells (i.e., having a eukaryotic DNA susbtrate).

Firstly, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Secondly, it is noted that most of the instant claims do not even require any DNA segment to be incorporated into the genome of the eukaryotic cell. Furthermore, regardless of the difference between a prokaryotic and a eukaryotic genome, λ Integrases catalyze recombinations though λ Integrase specific recombination sites. Hartley et al. taught clearly the use of a wild type λ Integrase in both *E.coli* cell lines as well as eukaryotic cells (col. 13, lines 35-55), and that Christ & Droge clearly taught that in the absence of IHF, wild-type Int and the two variants namely Int-h and Int-h/218

exclusively catalyze inversion (page 829, right hand column, top of the first full paragraph). Then why wouldn't these Integrase mutants function in eukaryotic cells to carry out any type of a recombination event through λ Integrase specific recombination sites? Or why would there not be a reasonable expectation of success?

Thirdly, the examiner notes that none of the instant claims requires the specific use of these mutant Integrases to carry out the deletion of any DNA segment in a eukaryotic type without the use of a Xis factor or Xis factor gene. Furthermore, Hartley et al. also teach the use of integrase in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL to form attP and attB.

As already noted above, an ordinary skilled artisan would be motivated to modify the method taught by Hartley et al. by utilizing the mutant λ Integrases, Int-h and Int-h/218 of Christ & Droge due to the advantages offered by the mutant integrases, at least that the mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than the wild-type Intergrase.

Accordingly, amended claims 29-30, 32-35, 44-45 and 58 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. in view of Christ & Droge for the reasons discussed above.

Amended claims 36-39 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. (US 5,888,732) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) as applied to claims 29-30, 32-35, 44-45, 49 and 58 above,

and further in view of Crouzet et al. (US Patent 6,143,530). ***This is a new ground of rejection.***

The combined teachings of Hartley et al and Christ & Droge have been discussed above. However, none of the references specifically teaches the modified method by providing to a eukaryotic cell a third DNA segment comprising an Int gene and a fourth DNA segment comprising Xis factor gene, wherein said third DNA segment and said fourth DNA segment comprises a regulatory sequence effecting a spatial and/or temporal expression of the Int gene or the Xis factor gene, even though Hartley et al teach the use of an Int in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL Please also note that the above modified method does not exclude the use of wild-type λ Integrase altogether in the method of Hartley et al, depending on whether the mutant Integrases would be employed in both recombination steps. With respect to claims 50-51, none of the references specifically teaches the modified method including the introduction of a DNA sequence comprising a Xis factor gene containing a regulatory sequence effecting a spatial and/or temporal expression of the Xis factor gene.

However, at the effective filing date of the present application Crouzet et al already taught a method for producing DNA molecules by excision from a plasmid or from a chromosome by site-specific recombination, wherein the site-specific recombination is carried out in a host cell (including eukaryotic cells such as yeasts, animal cells, plant cells, mammalian cells such as CHO, COS and mouse NIH3T3; col. 9, lines 48-60) or *in vitro*, and wherein the site-specific recombination is carried out by

means of various systems which lead to site-specific recombination between sequences (col. 3, line 27 continues to line 20 of col. 4; Figures 1-2). Specifically, Crouzet et al already disclosed that the gene or genes of interest flanked by the two sequences permitting site-specific recombination, positioned in the direct orientation in a vector, a phage or a virus, and the specific recombination sequences and recombinases used can belong to different structural classes, including the integrase family of bacteriophage λ and the attP and attB sequences catalyzed by the phage lambda integrase (col. 4, lines 21-52; col. 5, lines 32-41). More importantly, Crouzet et al teach that the recombinase used can be under the control of a promoter or a system of inducible promoters, and it can be carried by a plasmid, a phage or even in the non-therapeutic region of the recombinant DNAs (col. 7, line 45 continues to line 39 of col. 8).

It would have been obvious for an ordinary skilled artisan to further modify the method taught by Hartley et al and Christ & Droge by providing the eukaryotic cell a nucleic acid molecule encoding an Integrase and/or a protein Xis, operably linked to a regulatory promoter, instead of using Integrase protein and protein Xis as disclosed in the method of Hartley et al. for making a chimeric DNA *in vitro* and *in vivo*, in light of the teachings of Crouzet et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Crouzet et al already taught at least that the provision of an Integrase in the form of an expression cassette under the control of an inducible promoter or temperature-sensitive systems allows the induction of site-specific

recombination *in vivo* in a regulated manner by simply placing the cells in culture at the desired time under the conditions for the expression of the recombinase gene (at least col. 8, lines 3-17). Similarly, the provision of an Xis factor gene in the form of an expression cassette under the control of an inducible promoter or temperature-sensitive systems would also allow the induction of site-specific excision by Integrase in a regulated manner.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hartley et al., Christ & Droge, Crouzet al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claims 29-30, 32-33, 44-48 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS). ***This is a modified rejection with respect to the revised teachings of Christ & Droge below.***

Crouzet et al teach a method for producing therapeutic DNA molecules by excision from a plasmid or from a chromosome by site-specific recombination, wherein the site-specific recombination is carried out in a host cell or *in vitro*, and wherein the site-specific recombination is carried out by means of various systems which lead to site-specific recombination between sequences (col. 3, line 27 continues to line 20 of col. 4; Figures 1-2). Specifically, Crouzet et al disclose that the gene or genes of

interest flanked by the two sequences permitting site-specific recombination, positioned in the direct orientation in a vector, a phage or a virus, and the specific recombination sequences and recombinases used can belong to different structural classes, including the integrase family of bacteriophage λ and the attP and attB sequences catalyzed by the phage lambda integrase (col. 4, lines 21-52; col. 5, lines 32-41). The disclosed attB sequence is identical to SEQ ID NO:1 of the present application (see SEQ ID NO:6), and therefore the corresponding attP recombination sequence must have the same SEQ ID NO: 2 of the present application, or at least a derivative thereof. Additionally, Crouzet et al. teach that their genetic constructs can be used for the construct of cell hosts having disclosed elements integrated in their genomes (col. 4, lines 4-9, and Figure 1). Crouzet et al further teach that the recombinase used can be under the control of a promoter or a system of inducible promoters, and it can be carried by a plasmid, a phage or even in the non-therapeutic region of the recombinant DNAs (col. 7, line 45 continues to line 39 of col. 8), and that any type of host cell can be used including eukaryotic cells such as yeasts, animal cells, plant cells, mammalian cells such as CHO, COS and mouse NIH3T3 (col. 9, lines 48-60). Crouzet et al also disclose that their genetic constructs comprise one or more genes of interest such as the genes coding for enzymes, hormones, growth factors, apolipoproteins, tumor suppressor genes, suicide genes, natural or artifical immunoglobulin or an antigenic peptide (col. 13, lines 14-50).

Crouzet et al do not specifically teach the use of any modified λ Integrase, specifically Int-h or Int h/218 in their method of producing therapeutic DNA molecules,

even though they teach that any specific recombination sequences and appropriate recombinases can be used, including those belonging to the bacteriophage λ system.

However, at the effective filing date of the present application Christ & Droge already taught the mutant λ Integrases, Int-h and Int-h/218, that are capable of mediating substrate deletion through λ site-specific recombination in prokaryotes in the absence of co-factors Fis and Xis (see at least the abstract; page 829, right hand column, top and bottom of the first full paragraph). Christ & Droge further teach that the potential of these mutants to perform recombination in the absence of accessory factors is due to their enhanced affinity for core sites, and that Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase (page 827, left column, second full paragraph; page 828, left column, top of last paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Crouzet et al by utilizing specifically the mutant λ Integrases, Int-h and Int-h/218, of Christ & Droge in their method of producing therapeutic DNA molecules due to the advantages offered by the mutant integrases, at least the mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than the wild-type Intergrase.

An ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Christ & Droge, at least these mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 2/13/06 (pages 9-10) have been fully considered but they are respectfully not found persuasive.

Once again Applicants argue that Crouzet et al use exclusively the **wild-type** lambda integrase, while Christ & Droge relates exclusively to integrative and excisive attL/attR and attP/attB recombination performed in **prokaryotes**. There was no motivation for combining these two very distinct systems, and even if there were, there was no likelihood of success that they would be compatible, i.e., that the modified integrases of Christ & Droge would function in a eukaryotic system.

Please refer to the same examiner's response to the same Applicant's arguments for the rejections of claims 29-30, 32-35, 44-45, 49 and 58 above.

Amended claims 29 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) as applied to claims 29-30, 32-33, 44-48 and 58

above, and further in view of Capecchi et al. (US 5,464,764). ***This is a modified rejection with respect to the revised teachings of Christ & Droge above.***

The teachings of Crouzet et al. and Christ & Droge have been discussed above. However, neither Crouzet et al nor Christ & Droge teach that the first and/or the second DNA segment further comprising a sequence effecting integration of said first and/or second DNA segment into the genome of a cell by homologous recombination, even though Crouzet et al teach specifically that the genetic constructs can be used for the construct of cell hosts having disclosed elements integrated in their genomes (col. 4, lines 4-9, and Figure 1).

However, at the effective filing date of the present application Capecchi et al. already describe a well-known method and a positive-negative selector vectors comprising sequences to be introduced in the genome of a target cell by the homologous recombination approach (see abstract and Figure 1).

It would have been obvious for an ordinary skilled artisan to further modify the modified method of Crouzet et al and Christ & Droge by introducing the genetic construct in the form of a positive-negative selector vector described by Capecchi et al. into a target host cell capable of homologous recombination to incorporate their genetic construct in the genome of the host cell as specifically taught by Crouzet et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the approach taught by Capecchi et al. overcomes many problems associated with random integration, and that the gene of interest can be introduced into any predetermined region of the genome of a target host cell.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge and Capecchi et al, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 2/13/06 (page 10) have been fully considered but they are respectfully not found persuasive.

Applicants argue mainly that Capecchi et al. fails to address the issue whether modified integrases would work in eukaryotic cells to supplement the defects of Crouzet et al. and Christ & Droge. Additionally, Applicants argue that there was no motivation for combining the primary and secondary references and there was no likelihood of success that they would work together.

With respect to the defects of Crouzet et al and Christ & Droge, please refer to the same examiner's response to the same Applicant's arguments for the rejections of claims 29-30, 32-35, 44-45, 49 and 58 above.

With respect to the lack of motivation and no likelihood of success, as noted in the above rejection an ordinary skilled artisan would have been motivated to carry out the above modification because the approach taught by Capecchi et al. overcomes many problems associated with random integration, and that the gene of interest can be

introduced into any predetermined region of the genome of a target host cell. An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge and Capecchi et al, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Accordingly, amended claims 29 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) as applied to claims 29-30, 32-33, 44-48 and 58 above, and further in view of Capecchi et al. (US 5,464,764) for the reasons set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D
PATENT EXAMINER